further comprising a second recombinant DNA construct comprising a promoter operably linked to a reading frame coding for a signal peptide component and the heavy chain or the light chain of said chimeric antibody or CDR-grafted antibody or fragment thereof, such that upon co-expression of said first and second recombinant DNA constructs in the effector cell, the light and heavy chains of the chimeric antibody, CDR-grafted antibody or fragment thereof assemble to form a binding component which binds to a cell surface antigen on a target cell.

REMARKS

In the Office Action dated January 9, 2001, claims 11, 14, 20-31, 33-42, 46,47, 50 and 51 are pending in the above referenced application and claims 11, 14, 20-31, 33-42, 46,47, 50 and 51 stand rejected. Claims 14, 20, 25, 26, 27, 50 and 51 have been cancelled without prejudice, in order to expedite prosecution of this application. Claims 11, 21-24, 28-31, 33-36, 38-42, 46, and 47 have been amended to further clarify the subject matter of the invention. New claim 52 has been added and replaces claim 14. Support for the amendments is found throughout the specification and no new matter has been added. Applicants reserve the right to pursue the subject matter of the cancelled claims at a later date, e.g., in a divisional application.

Applicants respectfully request reconsideration of the application in light of the above amendments and the following discussion.

A petition for an extension of time of three (3) months for responding to the outstanding Office Action and the appropriate fee is enclosed herewith.

In the previous Office Action, the Examiner is requested a new Declaration that contains a claim for priority to application GB 9526131.9, in order to receive the benefit of the filing date of the GB9526131.9 application. This Declaration is submitted herewith.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

The Examiner has objected to claim 36 suggesting that the term "viral vector or a non-viral vector" should be changed to --vector--. Applicants respectfully submit that the claim is appropriate and provide basis for the claims that depend from claim 36.

Claims 11, 14, 20-31, 33-42, 46, 47, 50, and 51 stand rejected under 35 U. S. C. 112, second paragraph, as indefinite. Applicants respectfully disagree. However, in order to expedite examination of this case, the claims have been amended to address the examiner's rejections.

The Examiner objected to the phrase "capable of one type of extracellular interaction" in claim 11. This phrase has been deleted from claim 11 and has been replaced by the phrase "which binds a cell surface antigen on a target cell". It is believed that this amendment clarifies the meaning of the claim.

In response to the Examiner's objection to the phrase "in association with", this phrase has been deleted.

As suggested by the Examiner, the phrase "not naturally linked" has been deleted from claim 11 and the claims have been amended to recite that the DNA delivery system comprises a recombinant construct.

The phrase "derived from" has been deleted from the claims.

Claim 11 has been amended to recite the term "binding component" to provide antecedent basis for claims 11, 46 and 50.

New claim 52 has been added as rewritten claim 14. Claim 52 depends on claim 11, as suggested by the Examiner and clarifies that the light chain of the antibody and the heavy chain of the antibody which together make up the binding component may be found on different DNA constructs.

The rejections of claims 21 and 22 are moot since the term "binding component" has now been introduced into claim 11 and there is therefore antecedent basis for this term in claims 21 and 22.

The Examiner rejected claims 24, 26, 28 and 33-35 for the recitation of the phrase "all or part of". This phrase has now been deleted and the claims now refer to the whole entity "or a fragment thereof". It is clear from page 8, line 30 of the International application that fragments must retain substantially the same function as the starting component and cannot therefore include a single amino acid.

The Examiner rejected the phrase "capable of acting cooperatively" in claim 25. Claim 25 has now been deleted but the phrase was intended to mean that the cytoplasmic components are capable of acting together to stimulate signal transduction, as is now specified in claim 11.

Claim 26 has now been incorporated into claim 11. The reference to the "7 chain of a Fc receptor" has been corrected to read the "γ chain".

The objection to the term "binding component" in claim 31 has been overcome by the amendment of claim 11 to include antecedent basis for this term. In addition, claim 31 has been amended to clarify it.

Claim 38 has been amended to refer to a non-viral vector, as suggested by the Examiner.

The Examiner rejected claims 40-42 on the basis that the definition of the carrier was unclear. The term "carrier" has been replaced in all the claims by "means

for delivery of said construct to an effector cell." It is clear from the description that this is what was intended by the term "carrier" and it is believed that this amendment and the additional amendments to claims 40-42 obviate the rejection.

The Examiner's rejections of claims 50-51 are moot in view of the cancellation of these claims.

Applicants respectfully request reconsideration and withdrawal of the above rejection.

Claims 11, 14, 20-31, 33-42, 46, 47, 50, and 51 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons of record as based on a disclosure which is not enabling. The Examiner states that operably linked promoters considered critical or essential to the practice of the invention, but not included in the claims are not enabled by the disclosure. Applicants respectfully disagree with the Examiner's position.

The Examiner has rejected the claims stating that the claims are not enabling unless they recite the operable linkage of a promoter to the coding sequences. While Applicants disagree with the Examiner's position, claims 11 and 14 have been amended to recite the presence of a promoter, as suggested by the Examiner, in order to expedite prosecution of this application.

Claims 11, 14, 20-31, 33-42, 46, 47, 50, and 51 stand rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. Applicants respectfully traverse this rejection. The Examiner agrees that the specification is enabling for use in cultured cells of the embodiments recited in Examples 2-6 of the specification. It is the Examiner's position, however, that the specification does not provide enablement for the broad range of embodiments covered by the claims. The Examiner argues that the specification does not enable the skilled person to make and use the invention over the breadth of the claims.

Applicants respectfully disagree with the Examiner's position. The application clearly teaches one of ordinary skill in the art how to assess whether a cell signaling pathway is being activated by the chimeric receptor, regardless of which cytoplasmic signalling components are used.

While Applicants disagree with the Examiner's position and respectfully submit that the specification provides sufficient enablement, the above amendments to the claims obviate this rejection. Claim 11 has been amended to incorporate the cytoplasmic components previously listed in claim 26. Thus, amended claim 11 now recites a list of cytoplasmic components.

Claim 11 has also been amended to recite that the binding component is a chimeric or CDR-grafted antibody, an embodiment which was previously found in claim 20. Claim 20 has therefore been deleted.

In addition, claim 11 has been amended to recite that when the chimeric receptor is expressed in the effector cell and when the binding components bind to the cell surface antigen on the target cell, a cytoplasmic signalling pathway must be activated. Basis for this amendment can be found throughout the description since it is clearly the aim of the invention to activate cell signalling pathways in effector cells without the requirement for co-stimulation by MHC molecules. This property of stimulating signal transduction was previously covered in claim 25.

The examples in the specification teach the production of chimeric receptors comprising a humanized scFv, a transmembrane domain and two of the cytoplasmic domains recited in claim 11. The examples further demonstrate the expression of such chimeric receptors in cells and the ability of such chimeric receptors to activate a signalling pathway. The examples teach one of ordinary skill in the art how to assess whether a cell signalling pathway is being activated not only in Jurkat cells but also in cytotoxic T lymphocytes, monocytes and macrophages. The examples therefore provide detailed information on the construction of the DNA delivery system, transfection of said delivery systems into a range of cells and assessment of the expression of the

chimeric receptors. The examples also teach the person of ordinary skill in the art how to identify appropriate receptor intracellular domains for use in different types of cells by assessing activation of cell signalling pathways.

Accordingly, it is respectfully submitted that the specification provides enough information to enable a person of ordinary skill in the art to construct a chimeric receptor having the components and the properties claimed in claim 11 and dependent claims. It is also respectfully submitted that the specification, especially the examples, provides enough information to produce an effector cell comprising the DNA delivery system.

Applicants respectfully request reconsideration and withdrawal of the above rejection.

Claim 14 stands rejected under 35 U.S.C. 112, first paragraph, for lack of written description. Applicants respectfully traverse this rejection. In order to expedite prosecution of this case, Applicants have rewritten claim 14 as new claim 52. Applicants respectfully submit that this rejection has been obviated and request withdrawal of the rejection.

Claims 11, 14, 20-31, 33-38, 46, 47, 50, and 51 stand rejected under 35 U.S.C. 102(e) as being anticipated Roberts (US 5,712,149). Applicants respectfully traverse this rejection. Claim 11, as amended, recites that the binding component of the chimeric receptor encoded by the DNA delivery system is a chimeric antibody, a CDR-grafted antibody or a fragment thereof. Support for this amendment can be found on page 6, line 5 of the International application from which the current US application is derived. This section of the description teaches that both chimeric antibodies and engineered human antibodies may be used as binding components. In chimeric antibodies, the variable region of a first antibody is joined to the constant region of a second antibody. Generally, the variable region is from a murine monoclonal antibody and the constant region is from a human antibody. In engineered human antibodies, one or more CDRs and one or more framework residues derived from a non-human

antibody, generally a murine antibody, are embedded in a human framework. Furthermore, the examples set forth in the present application disclose the production and use of DNA delivery systems encoding chimeric receptors in which the binding component is a CDR-grafted antibody or an scFv derived from a CDR-grafted antibody.

The use of chimeric and engineered antibodies is clearly not contemplated by, or taught by, Roberts *et al.* The claims are therefore not anticipated by this reference.

Furthermore, it is noted that the use of chimeric and humanized antibodies as the binding components in the chimeric receptors of the present invention has a number of advantages over the use of monoclonal antibodies as proposed by Roberts *et al.* The chimeric receptors of the present invention have applications in the treatment of human diseases and conditions. However, murine monoclonal antibodies are naturally antigenic in humans, limiting their therapeutic potential. Ideally, the use of human monoclonal antibodies would prevent such antigenic responses. However, the production of human monoclonal antibodies has proved an elusive goal. Instead, the immune response can be minimized by using a chimeric antibody since the constant region of a chimeric antibody is human. Using CDR-grafted antibodies reduces the immune response still further since only the antigen binding portions of a murine monoclonal antibody are used and these are embedded in a human framework. Using chimeric and CDR-grafted antibodies as the binding component of the chimeric receptors of the current invention therefore increases the therapeutic potential of the DNA delivery systems encoding the receptors.

Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Claims 11, 14, 20-31, 33-36, 46, 47, 50, and 51 stand rejected under 35 U.S.C. 102(e) as being anticipated by Seed et al. (US 5,912,170). Applicants respectfully traverse this rejection.

The Examiner was not persuaded with Applicants argument submitted in the previous response that Seed *et al* does not disclose a chimeric receptor containing two

cytoplasmic components on the same chain. The Examiner cites Figure 1A and column 32, lines 53-55, of Seed *et al.* as teaching chimeric receptors having two or more intracellular signalling components which are not naturally linked. Applicants respectfully submit that the Examiner is mistaken in this assertion. Figure 1A simply discloses chimeric receptor constructs in which the extracellular domain of CD16 is joined to the transmembrane domain of CD7, which is joined in turned to the complete coding sequences of human Lck, murine Fyn, porcine syk or human ZAP-70. This is stated in column 19, lines 13-23. Each of these tyrosine kinases contains a kinase domain, an SH2 domain and an SH3 domain. Figure 1A therefore merely discloses the use of cytoplasmic domains which are linked in each of these molecules in nature. The section of column 32 cited by the Examiner indicates that it is not always necessary to use the full coding sequence of the tyrosine kinases but that portions may be used. There is, however, simply no suggestion that a portion of the cytoplasmic region of one tyrosine kinase could be linked to a portion of the cytoplasmic region of another tyrosine kinase.

The present claims, as amended, recite that the binding component is a CDR-grafted antibody, a chimeric antibody or a fragment thereof. There is no teaching in Seed *et al.* that chimeric or CDR-grafted antibodies could be used as binding components in the chimeric receptors.

The claims are not anticipated by Seed *et al.* Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Claims 11, 14, 20-31, 33-38, 46, 47, 50, and 51 stand rejected under 35 U.S.C. 102(a) as anticipated by Capon et al. (WO 96/24671). Applicants respectfully traverse this rejection.

In the response to the last office action, Applicants argued that the claims were novel over Capon *et al* on the basis that Capon *et al* discloses multispecific binding of chimeric receptors while the chimeric receptors of the present invention only bind to one component on the target cell. The Examiner rejected this argument on the

grounds that it was not clear that the chimeric receptors of the invention bound monospecifically.

The claims as amended recite that the binding component binds to a single cell surface antigen on a target cell. In addition, the amended claims recite that the binding component is a chimeric antibody or a CDR-grafted antibody. The amended claims are not anticipated by Capon *et al.* Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

The Examiner has cited U.S. 6,103,521 as prior art made of record, but not relied upon. Applicants will not address this reference at this time. However, Applicants reserve the right to do so at a later date, if necessary.

The present amendment was not submitted at an earlier date because the Examiner's rejections were believed to have been fully met by the amendments and remarks made in the response to the last Office Action. Thus, this amendment is presented for further clarification in view of the Examiner's position and this response represents the Applicants' only opportunity to make the present amendments and remarks a part of the record in this application.

In view of the above amendment and discussion, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited. Should the Examiner wish to discuss

the above amendment made herein, the undersigned attorney would appreciate the opportunity to do so. Thus the Examiner is hereby invited to call the undersigned, collect at the number shown below.

Respectfully submitted,

Date: July 9, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

11. (Twice amended) A DNA delivery system comprising ~~DNA in association with a carrier, said DNA coding for a recombinant chimeric receptor capable of one type of extracellular interaction and wherein said DNA codes in reading frame for~~ a recombinant DNA construct and a means for delivery of said construct to an effector cell, said recombinant DNA construct coding for a chimeric receptor which binds a cell surface antigen on a target cell, wherein said recombinant DNA construct comprises a promoter operably linked to a reading frame coding for:

i) a signal peptide component;

ii) ~~an antibody or antigen binding~~ a binding component comprising a chimeric antibody, a CDR-grafted antibody or a fragment thereof;

iii) a transmembrane component;

iv) two or more different cytoplasmic signalling components ~~which are not naturally linked, and wherein at least one of said cytoplasmic~~ selected from the group consisting of the cytoplasmic domains of a zeta, eta or epsilon chain of the T-cell receptor, CD28, the γ chain of a Fc receptor, a cytokine receptor, a colony stimulating factor receptor, a tyrosine kinase or an adhesion molecule, B29, MB-1 CD3 delta, CD3 gamma, CD5 or CD2, or a fragment thereof, wherein at least one of said two cytoplasmic signaling components is derived from a membrane spanning polypeptide; and optionally

v) one or more spacer regions linking any two or more of said i) to iv) components wherein when said chimeric receptor is expressed in the effector cell and the binding component binds the cell surface antigen on the target cell, a signal is transduced in the effector cell via the cytoplasmic signalling components.

Please cancel claim 14, without prejudice.

Please cancel claim 20, without prejudice.

21. (Twice amended) The DNA delivery system according to claim 11 wherein the binding component is a chimeric or CDR-grafted single chain Fv fragment.

22. (Twice amended) The DNA delivery system according to claim 11 wherein the binding component is a chimeric or CDR-grafted Fab' fragment.

23. (Twice amended) The DNA delivery system according to claim 11 wherein the transmembrane component is ~~derived from all or part of~~ the alpha, beta or zeta chain of the T-cell receptor, CD28, CD8, CD4, a cytokine receptor or a colony stimulating factor receptor, or a fragment thereof.

24. (Twice amended) The DNA delivery system according to Claim ~~11~~ 23 wherein the transmembrane component is derived from all or part of CD28.

Please cancel claim 25, without prejudice.

Please cancel claim 26, without prejudice.

Please cancel claim 27, without prejudice.

28. (Twice amended) The DNA delivery system according to Claim ~~26~~ 23 wherein the cytoplasmic signalling components ~~are derived from all or part of~~ comprise CD28 or the zeta chain of the T-cell receptor or a fragment thereof.

29. (Twice amended) The DNA delivery system according to claim 11 wherein the cytoplasmic signalling components are in any ~~orientation~~ order relative to one another.

30. (Twice amended) The DNA delivery system according to claim 11 wherein said DNA coding for components i) to iv) additionally codes for one or more spacer regions linking the ~~antibody or antigen~~-binding component or fragment thereof ii) and the transmembrane component iii).

31. (Twice amended) The DNA delivery system according to ~~C~~claim ~~11~~ 52 wherein two or more different spacer regions link the binding component ii) and the transmembrane component iii), ~~both regions either being coded for by one DNA sequence or when a first and second DNA sequence is present one region being coded for by said first DNA~~ one region being coded for by said first recombinant DNA construct and the other different region being coded for by said second recombinant DNA construct.

33. (Twice amended) The DNA delivery system according to claim ~~30~~ wherein the spacer region is ~~derived from all or part of~~ the extracellular region of CD8, CD4 or CD28 or a fragment thereof.

34. (Twice amended) The DNA delivery system according to claim ~~30~~ 11 wherein the spacer region is ~~all or part of~~ an antibody constant region or a fragment thereof.

35. (Twice amended) The DNA delivery system according to claim ~~30~~ 11 wherein the spacer region is ~~derived from all or part of~~ an antibody hinge region or a fragment thereof linked to all or part of the extracellular region of CD28 or a fragment thereof.

36. (Twice amended) The DNA delivery system according to claim 11 wherein the ~~carrier~~ means for delivery of said construct is a viral vector or a non-viral vector.

38. (Twice amended) The DNA delivery system according to Claim 36 wherein the ~~carrier~~ non-viral vector is a targeted non-viral vector.

39. (Twice amended) The DNA delivery system according to Claim 11 wherein the ~~carrier~~ means for delivery of said construct is an antibody targeted liposome.

40. (Twice amended) The DNA delivery system according to Claim 11 wherein the ~~carrier is an antibody targeted~~ recombinant DNA construct is condensed DNA and the means for delivery of said construct is antibody targeting of said condensed DNA.

41. (Twice amended) The DNA delivery system according to Claim 11 wherein the ~~carrier is an antibody targeted~~ recombinant DNA construct is protamine or polylysine condensed DNA and the means for delivery of said construct is antibody targeting of said protamine or polylysine condensed DNA.

42. (Twice amended) The DNA delivery system according to Claim 11 wherein ~~the carrier is antibody targeted naked DNA~~ the recombinant DNA construct is naked DNA and the means for delivery of said construct is antibody targeting of said naked DNA.

46. (Twice amended) An effector cell selected from a lymphocyte, a dendritic cell, a B-cell, a haematopoietic stem cell, a macrophage, a monocyte or a NK cell, transfected with ~~a~~ the DNA delivery system ~~comprising DNA in association with a carrier said DNA coding for a recombinant chimeric receptor capable of one type of extracellular interaction and wherein said DNA codes in reading frame for:~~

~~i) a signal peptide component;~~

~~ii) an antibody or antigen binding fragment thereof;~~

~~iii) a transmembrane component;~~

~~iv) two or more different cytoplasmic signalling components which are not naturally linked, and wherein at least one of said cytoplasmic components is derived from a membrane spanning polypeptide; and optionally~~

~~v) one or more spacer regions linking any two or more of said i) to iv) components~~ according to claim 11.

47. (Amended) An effector cell according to Claim 46 ~~which~~, wherein the effector cell is a cytotoxic T-lymphocyte.

Please cancel claim 50, without prejudice.

Please cancel claim 51, without prejudice.

Please add the following claim:

--52. A DNA delivery system according to claim 11 wherein the recombinant DNA construct encodes either the light chain or the heavy chain of said chimeric antibody or CDR-grafted antibody or a fragment thereof, said DNA delivery system further comprising a second recombinant DNA construct comprising a promoter operably linked to a reading frame coding for a signal peptide component and the heavy chain or the light chain of said chimeric antibody or CDR-grafted antibody or fragment thereof, such that upon co-expression of said first and second recombinant DNA constructs in the effector cell, the light and heavy chains of the chimeric antibody, CDR-grafted antibody or fragment thereof assemble to form a binding component which binds to a cell surface antigen on a target cell.--